## REMARKS

### I. Status Summary

Claims 1-6, 8-13 and 30 are pending in the present application and are presently examined. The U.S. Patent and Trademark Office (hereinafter "the Patent Office") has rejected claims 1-6, 8-13 and 30.

Claim 30 is rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claim fails to satisfy the enablement requirement.

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pietu et al. (*Genome Research*, Vol. 6, pp. 492-503, 2000; hereinafter "Pietu et al.").

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. (*Mol. Cell Biol.*, Vol. 20, No. 21, pp. 8157-67, November 2000; hereinafter "Jelinsky et al.") in view of U.S. Patent Application Publication No. 2007/0037144 to Wohlgemuth et al. (hereinafter "Wohlgemuth et al.").

Claims 8-13 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. in view of Wohlgemuth et al. in further view of U.S. Patent No. 5,830,645 to Pinkel et al. (hereinafter "Pinkel et al.").

Claims 1, 2, 8 and 9 have been amended. Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 2, lines 21-32; page 3, lines 21-33; page 17, lines 17-31; page 20, line 11, through page 24, line 23; and in original claims 1 and 8. Accordingly, no impermissible new matter has been added by this claim amendment.

New claims 31 and 32 have been added. Support for new claims 31 and 32 can be found throughout the specification as originally filed, including particularly original claims 1 and 8, and Figures 1-4. No new matter has been added.

Reconsideration of the application based on the amendments and arguments set forth herein is respectfully requested.

## II. Discussion of Presently Disclosed and Claimed Subject Matter

Microarray analysis for gene expression has become more common now that sequence information for DNA is readily available. One way of obtaining information about genes involves the use of an array of probes, e.g. a microarray. One type of array of probes is made on a silicon array of cells, and includes DNA fragments or oligomers attached at each cell. The DNA probe is used to hybridize RNA transcripts labeled with fluorophores, or more typically their cDNA counterparts, produced by a target gene. The DNA probe in the array is exposed to the RNA transcripts or cDNAs, which then attach or hybridize to the DNA probes if they match. Unattached RNAs or cDNAs are washed away, and the array is exposed to laser light causing the attached RNA associated fluorophores to fluoresce. The amount of fluorescence is measured and is representative of the expression level of the gene.

Because probes exhibit different sensitivities it is difficult to compare results from different probes, which in turn hinders accurate mining and systematic integration of microarray data. This problem can preclude accurate comparison of expression levels between different genes, the determination of absolute expression values, and the elimination of cross-hybridization signals. *See*, e.g., page 1 of the specification of the instant U.S. patent application as originally filed for further details.

Applicants respectfully submit that the presently disclosed and claimed subject matter is believed to address this problem. This is accomplished by calculating correction factors, e.g. correction coefficients and/or uncertainty factors, for individual probes contemplated for use in microarray analysis of gene expression. The correction factors for each probe are derived from analysis of genomic DNA hybridization signals. If a probe is then employed in a microarray analysis, e.g. a cDNA microarray assay for measuring gene expression, the intensity of the signals detected in that analysis can be corrected using each individual probe's predetermined correction factor. As such, the presently claimed methods provide for the calculation of correction coefficients for individual probes contemplated for use in microarray analysis.

By way of example and not limitation, individual probes used on microarrays are re-scaled and corrected with a set of probe dependent coefficients derived from genomic DNA ("gDNA") hybridization signals. A dynamic range for gDNA binding is determined by measuring a concentration signal curve. Signals for each probe are measured during multiple hybridizations within a linear range. Concentration insensitive probes are then found for two sets of experiments. In some embodiments, probes are discarded based on a threshold compared to their standard deviation divided by their average in each set. In one embodiment, the threshold for each set is different. The threshold for the sets varies between about 0.34 and 0.07. A correlation coefficient is used in further embodiments to discard probes. An intersection for discarded probes for the two sets is found and used to normalize probe intensities from different hybridizations globally.

An average and standard deviation is calculated for the hybridization signals observed on each oligo, and the correction coefficient for each oligo is calculated by requiring its signal average to be equal to a constant. An uncertainty coefficient is calculated for each oligo as the ratio between the standard deviation and average.

When employed in mircroarray analysis for gene expression, for example, the correction coefficient for each probe is used to calculate a corrected intensity for each signal corresponding to that probe. Stated another way, each of the signal intensities is corrected using its probe's predetermined correction coefficient that was derived from a separate genomic DNA hybridization analysis. *See*, e.g., page 2 of the specification as originally filed for further details.

## III. Response to the Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 30 is rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claim fails to satisfy the enablement requirement. The Patent Office contends that the description does not provide detailed guidance for calculating gene expression from genomic DNA hybridization array data. The Patent Office contends that the predictability of calculating gene expression only from

genomic DNA hybridized to arrays is unknown in the prior art. As such, the Patent Office contends that an unpredictable amount of experimentation would be required to practice the claimed invention.

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

As set forth in the above discussion of the presently disclosed and claimed subject matter and throughout the specification as originally filed, the genomic DNA hybridization signals are used for the calculation of the correction factors, e.g. correction coefficients, for each oligonucleotide probe. If a probe is subsequently employed in a microarray analysis, e.g. a cDNA microarray assay, each microarray signal indicative of gene expression can then be corrected using each individual probe's predetermined correction factor. As such, in contrast to the assertion by the Patent Office and as would be appreciated by one of ordinary skill in the art upon review of the instant disclosure, the gDNA is not used solely for calculating gene expression. Rather, in the present claims the genomic DNA hybridization data is used for calculating individual probe correction factors. The probes can then be used in microarray analsysis, e.g. cDNA microarray analysis, for the determination of gene expression, wherein the gene expression data can be corrected using the calculated each individual probe correction factors. Thus, the assertion upon which the instant enablement rejection is based appears to be unfounded.

Notwithstanding the above and without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 1, from which claim 30 ultimately depends, has been amended to further clarify the claimed subject matter. In particular, claim 1 has been amended to recite, *inter alia*, "calculating a correction coefficient for each oligo probe based on the measured signals from the genomic DNA hybridizations". Present claim 1 also recites, "employing the oligo probes with calculated correction coefficients in a microarray for determining gene expression; and correcting the signal for each oligo probe on the gene expression microarray

using the calculated correction coefficient, wherein the corrected oligo probe hybridization signals derived from the gene expression microarray are outputted to a computer memory. Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 2, lines 21-32; page 3, lines 21-33; page 17, lines 17-31; page 20, line 11, through page 24, line 23; and in original claim 1. Accordingly, no impermissible new matter has been added by this claim amendment.

Furthermore, without acquiescing to the contentions of the Patent Office, claim 30 has been amended to clarify that the oligo probes are used to detect the expression level of the gene. Support for the amendment to claim 30 can be throughout the specification as originally filed, and particularly in Figure 2. No new matter has been added.

Consequently, it is respectfully submitted that the rejection of claim 30 under 35 U.S.C. §112, first paragraph, has been addressed. It is therefore respectfully requested that the rejection of claim 30 under 35 U.S.C. §112, first paragraph, be withdrawn. A Notice of Allowance is also respectfully requested.

## IV. Response to the Rejections Under 35 U.S.C. § 102(b)

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pietu et al. The Patent Office contends that Pietu et al. teaches each and every element of the rejected claims. Applicants respectfully traverse the rejections under § 102(b).

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

Initially, without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 1 has been amended herein to further clarify the claimed subject matter. In particular, claim 1 has been amended to recite, *inter alia*, "calculating a correction coefficient for each oligo probe based on the measured

signals from the genomic DNA hybridizations". Present claim 1 also recites, "employing the oligo probes with calculated correction coefficients in a microarray for determining gene expression; and correcting the signal for each oligo probe on the gene expression microarray using the calculated correction coefficient, wherein the corrected oligo probe hybridization signals derived from the gene expression microarray are outputted to a computer memory. Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 2, lines 21-32; page 3, lines 21-33; page 17, lines 17-31; page 20, line 11, through page 24, line 23; and in original claim 1. Accordingly, no impermissible new matter has been added by this claim amendment.

Applicants respectfully submit that Pietu et al. fails to teach a method of calculating a correction coefficient for each oligo probe based on the measured signals from the genomic DNA hybridizations, as presently claimed. Rather, Pietu et al. is, at best, directed to normalizing the signal intensities obtained from the microarray hybridization and makes no mention of calculating correction coefficients for the probes themselves. Applicants respectfully refer to the discussion of the presently disclosed and claimed subject matter hereinabove regarding this distinction.

Further, while Pietu et al. does mention the use of genomic DNA probes, it is in the context of detecting clones harboring repetitive sequences, not for correcting oligo probe hybridization signals as presently claimed. *See*, e.g., page 495, right column, of Pietu et al. Accordingly, applicants respectfully submit that Pietu et al. fails to anticipate each and every element of claim 1, or claims 2-4 depending therefrom.

It is therefore respectfully requested that Pietu et al. as a reference be withdrawn, and hence, that the rejection of claims 1-4 under 35 U.S.C. §102(b) be withdrawn. A Notice of Allowance is also respectfully requested.

## V. Response to the Rejections Under 35 U.S.C. § 103(a)

### V.A. Rejection of Claims 1-6 Over Jelinsky et al. and Wohlgemuth et al.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. (*Mol. Cell Biol.*, Vol. 20, No. 21, pp. 8157-67, November 2000; hereinafter "Jelinsky et al.") in view of U.S. Patent Application Publication No. 2007/0037144 to Wohlgemuth et al. (hereinafter "Wohlgemuth et al."). The Patent Office admits that Jelinsky et al. fails to teach the individual calculation of correction coefficients for individual probes where the average signal of the individual probes is made to equal a constant. However, the Patent Office contends that Wohlgemuth et al. compensates for this deficiency in Jelinsky et al.

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

Initially, without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 1 has been amended herein to further clarify the claimed subject matter. In particular, claim 1 has been amended to recite, *inter alia*, "calculating a correction coefficient for each oligo probe based on the measured signals from the genomic DNA hybridizations". Support for this amendment can be found throughout the claims and specification as filed, and in particular in original claim 1. Accordingly, no impermissible new matter has been added by this claim amendment.

Neither Jelinsky et al. nor Wohlgemuth et al., alone or in combination, teach a method of calculating a correction coefficient for each oligo probe based on the measured signals from the genomic DNA hybridizations, as presently claimed. Rather, Jelinsky et al. is, at best, directed to scaling the intensity data obtained from a cRNA microarray analysis, not calculating a correction coefficient for each oligo probe based on the measured signals from the genomic DNA hybridizations.

Wohlgemuth et al., at best, appears to correct probe signal for background noise for purposes of selecting expression data for analysis. *See*, paragraph [0207] of Wohlgemuth et al. The Patent Office contends that Wohlgemuth et al., at paragraph [0207], teaches that an average and standard deviation for the signals observed for each probe are calculated. Applicants respectfully disagree. Paragraph [0207] refers to correcting the intensity of signals acquired from microarray analysis employed for gene expression. There is no mention of "probe" or a method of calculating a correction coefficient for each oligo probe based on the measured signals from the genomic DNA hybridizations.

Furthermore, the alleged scaling of the data in paragraph [0212] is not believed to be tantamount to correcting oligo probe hybridization signals, comprising calculating a correction coefficient for each oligo probe, as recited in claim 1. In particular, the scaling referenced in paragraph [0212] is not believed to be based upon individual probe correction coefficients, but rather, the median, the mean, the trimmed mean, or percentile of the entire dataset.

Finally, the Patent Office refers to paragraph [0091] of Wohlgemuth et al. to support the contention that Wohlgemuth et al. teach DNA that is genomic DNA. Indeed, Wohlgemuth et al. mentions genomic DNA at paragraph [0091]. However, when read in context, there is no teaching or suggestion that Wohlgemuth et al. employs this genomic DNA in a hybridization from which correction coefficients for each oligo probe are calculated. As such, it appears that the Patent Office is inappropriately relying upon a selective reading of Wohlgemuth et al. to support the instant rejection.

Therefore, applicants respectfully submit that Jelinsky et al. and Wohlgemuth et al., alone or in combination, fail to teach each and every element of claim 1. Given that claims 2-6 depend either directly or indirectly from claim 1, they too are believed to be distinguished from the cited references.

Consequently, it is respectfully submitted that the rejection of claims 1-6 under 35 U.S.C. §103(a) as being obvious over Jelinsky et al. in view of Wohlgemuth et al. has been addressed. It is therefore respectfully requested that the rejection of claims 1-6 under 35 U.S.C. §103(a) be withdrawn. A Notice of Allowance is also respectfully requested.

V.B. Rejection of Claims 8-13 Over Jelinsky et al., Wohlgemuth et al. and Pinkel et al.

Claims 8-13 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. in view of Wohlgemuth et al. in further view of U.S. Patent No. 5,830,645 to Pinkel et al. (hereinafter "Pinkel et al."). Applicants respectfully traverse the rejections under § 103(a).

Applicants respectfully refer to the discussion hereinabove regarding the failure of Jelinsky et al. and Wohlgemuth et al. to teach each and every element of the claim 1. Applicants respectfully submit that Jelinsky et al. and Wohlgemuth et al. fail to teach each and every element of claim 8 for at least the same reasons. Furthermore, applicants respectfully submit that Pinkel et al. fails to compensate for the deficiency in the combined teachings of Jelinsky et al. and Wohlgemuth et al. with respect to claim 8.

Therefore, applicants respectfully submit that Jelinsky et al., Wohlgemuth et al. and Pinkel et al., alone or in combination, fail to teach each and every element of claim 8. Given that claims 9-13 depend either directly or indirectly from claim 8, they too are believed to be distinguished from the cited references.

Consequently, it is respectfully submitted that the rejection of claims 8-13 under 35 U.S.C. §103(a) as being obvious over Jelinsky et al. in view of Wohlgemuth et al. and further in view of Pinkel et al. has been addressed. It is therefore respectfully requested that the rejection of claims 8-13 under 35 U.S.C. §103(a) be withdrawn. A Notice of Allowance is also respectfully requested.

## DISCUSSION OF NEW CLAIMS

New claims 31 and 32 have been added. Support for new claims 31 and 32 can be found throughout the specification as originally filed, including particularly in original claims 1 and 8, and Figures 1-4. No new matter has been added.

Applicants respectfully submit that new claims 31 and 32 are believed to be patentable over the cited references for at least the reasons stated hereinabove. Applicants respectfully submit the new claims 31 and 32 are believed to be in condition for allowance and respectfully request a Notice of Allowance.

## CONCLUSION

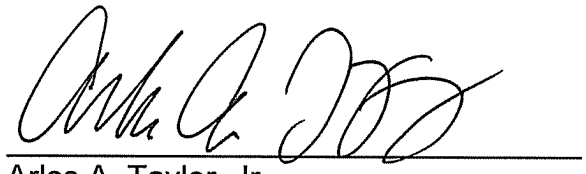
In light of the above amendments, remarks and the enclosed 131 affidavit, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any additional fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 05/04/2009 By: 

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